REMARKS

Claims 5 and 6 are pending in the instant application. Claims 5 and 6 have been rejected. Claim 5 has been amended. Claim 6 has been canceled in light of amendments to claim 5. New claim 9 has been added. No new matter is added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims 5-6 under 35 U.S.C. § 112, first paragraph - Written Description

The rejection of claims 5-6 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time application was filed, had possession of the claimed invention has been maintained. The Examiner suggests that a generic statement such as "non-internalizable antibody" is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of being non-internalizable. The Examiner has acknowledged applicant to be in possession of a method for dissolution of fibrin clots by administering a non-internalizable antibody to

ICAM-1 and a fibrinolytic or anticoagulant. However, the Examiner suggests that Applicants is not in possession of the method as claimed for augmenting local anti-thrombotic potential of endothelium and dissolving of intravascular blood clots in the pulmonary vasculature of an animal comprising intravenously administering to the animal a fibrinolytic or anticoagulant agent conjugated with an antibody which binds any antigen on the luminal surface of the vascular endothelium without subsequent internalization into endothelial cell. In particular the Examiner suggests that Applicants have disclosed only anti-ICAM-1 monoclonal antibody.

Applicants respectfully traverse this rejection.

At the outset, Applicants respectfully disagree with the Examiner's assertion that the genus of antibodies is only distinguished based upon the property of being non-internalizable. The claims of the instant application were amended in the last response to be drawn to a method wherein the antibody binds to an antigen on the luminal surface of the vascular endothelium without subsequent internalization into endothelial cells. Accordingly antibodies of the claimed genus are distinguishable based upon properties of non-internalization into endothelial cells **and** binding to an antigen on the luminal

surface of the vascular endothelium.

Arguments presented in the last response by Applicants regarding the fact that sufficient structural and functional details of the antibodies were taught in the patent application to support a genus were found unpersuasive as the Examiner suggests that "there is no described or art-recognized correlation or relationship between the structure of the invention, non-internalizable antibody that binds to an antigen on the luminal surface of the vascular endothelium, and it's targeting delivery function."

Applicants agree with the Examiner that there was no "art-recognized" correlation.

However, Applicants respectfully disagree with the Examiner that the relationship or correlation between the structure of the invention, a non-internalizable antibody that binds to an antigen on the luminal surface of the vascular endothelium and it's targeting delivery function, is not described sufficiently in the specification.

The relationship or correlation between the structure and function of the antibodies as claimed and their function in targeting and delivery of a therapeutic are set forth not only in the definition of non-internalizable antibody at page 9, lines 9-

16 of the specification but also in the detailed experiments described for distinguishing internalized antibodies from antibodies not internalized. For example, the definition for non-internalizable antibody states that "the antibody binds to an antigen on the luminal surface of the pulmonary vasculature" thus defining how the function of the antibody, namely to bind to an antigen on the luminal surface of the pulmonary vasculature, will target an agent conjugated thereto to the pulmonary vasculature. Further, this definition for non-internalizable antibody states that the antibodies are "determined not to be internalized by cultured human endothelial cells as described in the application and/or is shown to be temperature independent in pulmonary uptake experiments in isolated lung perfusions" thus defining how the function of non-internalization correlates again to the function of targeted delivery. Further, at page 6, line 13 through page 7, line 4, Applicants outline experiments for determining internalization of various antibodies and prolongation of these antibodies on the luminal surface and results which the inventors have indicated to be indicative of internalization versus non-internalization of the various antibodies and prolongation on the luminal surface. Thus, contrary to the Examiner's suggestion, the instant specification clearly describes the correlation or

relationship between the structure of the non-internalizable antibodies and their ability to target and deliver therapeutic agents to the pulmonary vasculature.

In an earnest effort to be responsive to the Examiner, Applicants have canceled claim 6 and added new claim 9 drawn to the subject matter acknowledged by the Examiner to meet the written description requirements of 35 U.S.C. § 112, first paragraph.

However, reconsideration and withdrawal of this rejection as it pertains to pending claim 5 is respectfully requested in view of the above remarks and the teachings of the instant specification clearly supportive of this claim.

II. Rejection of Claims 5-6 under 35 U.S.C. § 112, first paragraph - Lack of Enablement

Claims 5-6 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner has acknowledged the specification to be enabling for dissolution of fibrin clots by administering a non-internalizable antibody to ICAM-1 and a fibrinolytic or anti-coagulant. However, the Examiner suggests that the specification does not reasonably provide enablement for a method of augmenting local anti-thrombotic potential of

endothelium and dissolving of intravascular blood clots in the pulmonary vasculature of an animal comprising intravenously administering to the animal a fibrinolytic or anticoagulant agent conjugated with an antibody which binds any antigen on the luminal surface of the vascular endothelium without subsequent internalization into endothelial cell.

Applicants respectfully traverse this rejection.

As discussed in Section I, supra, Applicants have canceled claim 6 and added new claim 9 drawn to a the subject matter acknowledged by the Examiner to be enabled by the instant specification.

Further, with respect to claim 5, while Applicants disagree with the Examiner's suggestion that the specification is not enabling for preventative methods, in an earnest effort to advance the prosecution of this case, Applicants have deleted the phrase "augmenting local anti-thrombotic potential of endothelium".

With respect to use of non-internalized antibodies other than anti-ICAM-1, MPEP § 2164.02 clearly states that for a claimed genus, representative examples together with a statement applicable to the genus as well will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the

art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. As further stated in MPEP §2164.02, proof of enablement will be required only where adequate reasons are advanced by the Examiner to establish the a person skilled in the art could not use the genus as whole without undue experimentation. No such reasoning has been provided by the Examiner in the instant rejection.

In contrast, Applicants provided in the last response a publication evidencing the claimed method to be effective with another antibody which binds to an antigen on the luminal surface of the vascular endothelium without subsequent internalization into endothelial cells. The Examiner acknowledged receipt of this reference and its support for use of the non-internalizable anti-GP85 antibody, an antibody different from ICAM-1 antibody which binds to a different antigen on the luminal surface of the vascular endothelium without subsequent internalization into endothelial cells. This reference was dismissed by the Examiner, however, because the anti-GP85 antibody was not specifically disclosed in the specification.

Applicants respectfully disagree.

The mere fact that the phrase "anti-GP85 antibody" was not

disclosed in the patent application upon filing does not undermine the teachings of this reference confirming that other antibodies which bind to an antigen on the luminal surface of the vascular endothelium without subsequent internalization into endothelial cells, when conjugated to an anti-thrombotic agent, provide effective methods for clot dissolution. This specific antibody was clearly encompassed with Applicants' broader definition of non-internalizable antibodies and in enabled by the teachings of the instant specification.

Thus, reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph for lack of enablement is respectfully requested.

III. Rejection of Claims 5 and 6 under 35 U.S.C. § 103(a)

Claims 5 and 6 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Bowes et al. (Neurology 1995) in view of Imaizumi (Transpl. Proc. 1994), Mulligan et al. (Amer. J. Pathol. 1993) and Panes (Amer. J. Physiol. 1995), and further in view of Runge et al. and Torchilin et al. and Muzykantov et al. (BBA 1986) , and Muzykantov et al. (Amer. J. Physiol. 1996).

Applicants respectfully traverse these rejections.

At the outset, Applicants respectfully disagree with the Examiner's characterization of the teachings of the prior art.

The Examiner states at page 7 of the Office Action that:

> [g]iven that the conjugation of a drug (such as tPA) can be efficiently directed to the site of a thrombus by conjugation, i.e. chemical modification, an anti-fibrin mAb which result in both more potent and more selective thrombolysis taught by Runge et al. and given that anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature, i.e. binds to the luminal surface of the endothelium and is not internalized as taught by Mulligan et al. . . . "

No where in the Mulligan reference, however, is it taught that ICAM-1 mAb 1A29 is "not internalized".

Instead, as clearly taught in the specification at page 4, lines 8-10 and further at page 6, lines 6-11, Applicants, during reduction to practice of the instant invention, were the first to demonstrate that anti-ICAM-1 antibodies were not internalized but rather remained bound to the external surface of the pulmonary endothelial cells for a prolonged period of time.

MPEP § 2143 states that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations.

Claims of the instant application are drawn to methods of administering a non-internalizable antibody conjugated to an fibrinolytic or anticoagulant agent to dissolve intravascular blood clots in the pulmonary vasculature of an animal and to dissolve fibrin clots (acknowledged by the Examiner to be enabled and supported by the written description of the specification).

In contrast, all cited prior art references relating to fibrinolytic agents disclosed experiments with agent alone versus agent co-administered with an antibody or agent conjugated to a different, internalized antibody. References relating to anti-ICAM-1 are silent with respect to internalization of the antibody. In none of the cited reference were the effects of conjugating a thrombolytic agent with non-internalized antibody targeted to an antigen of the endothelium examined, disclosed or discussed. In fact, none of the cited references examined, disclosed or even discussed internalization characteristics of antibodies and a lack thereof in providing a therapeutic approach for fibrinolytic agents.

Therefore, the cited combination of prior art references does not provide the requisite teaching or suggestion to modify their teachings to arrive at the present invention. Further, these references provide no reasonable expectation that

antibodies such as ICAM-1 are not internalized. These references also provide no reasonable expectation of success that non-internalized antibodies such as ICAM-1 when conjugated to a fibrinolytic agent would remain bound to the external surface of the pulmonary endothelial cells for a prolonged period of time. Finally, these references provide no reasonable expectation that a fibrinolytic or anticoagulant agent, when conjugated to a non-internalized antibody would remain therapeutically active for prolonged periods in the lumen, particularly when it was well known in the art that anticoagulants and fibrinolytics undergo inactivation and elimination in the bloodstream. See page 1, lines 16-17 of the instant specification.

Therefore, the cited combination of prior art cannot render obvious the pending claims.

Withdrawal of these rejections under 35 U.S.C. § 103(a) is therefore respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Kathleen A. Tyrrell
Registration No. 38,350

Date: May 6, 2004

LICATA & TYRRELL P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515